

## **REMARKS**

### **Claim Status**

Claims 61-79 are pending in the application. Claims 67-79 were withdrawn by the Examiner as being drawn to a non-elected invention. Certain of the withdrawn claims have been amended to preserve Applicants' right to rejoinder. Claims 61 and 70 have been amended. Claim 62 has been cancelled.

### **Claim Amendments**

Claims 61 and 70 have been amended by including the subject matter of cancelled Claim 62 and by replacing a mean content of carbonic diester substituents per HES molecule from 1:1 to 4:1. Support for this amendment can be found, for example, in Claim 62 and in the specification on page 10, line 16.

Claim 62 has been cancelled.

### **Specification Amendments**

The specification has been amended to correct typographical errors and delete improperly referenced claim numbers.

### **Rejection of Claims 61-66 under 35 U.S.C. §112, First Paragraph**

Claims 61-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserted that Claims 61-66, being drawn to an aprotic-solvent-soluble carbonic diester of hydroxyethyl starch (HES), are not supported in the instant specification since there appears to be no mention of a carbonic diester of hydroxyethyl starch which is soluble in aprotic solvents.

Contrary to the Examiner's assertion, one of skill in the art, based on the teachings of the specification, would know that the carbonic diester of hydroxyethyl starches, as claimed, are soluble in aprotic solvents. The Examiner's attention is drawn to page 11, lines 4-20 of the instant specification for support that the claimed carbonic diesters are soluble in the aprotic solvents, reproduced herein for the Examiner's convenience (*emphasis added*):

The solutions obtained by the above-described reaction can be used in the coupling reactions without isolation of the carbonic acid diesters. Since, generally, the volume of the pre-activated carbonic acid diesters in the aprotic solvent is low, compared with the target protein dissolved in the buffer volume, the amounts of aprotic solvent generally do not interfere. Preferred solutions comprise at least 10% by weight of carbonic acid diesters, preferably at least 30% by weight of carbonic acid diesters, and particularly preferably at least 50% by weight of carbonic acid diesters.

The carbonic acid diesters can be precipitated from the solution in aprotic solvent, for example DMF, by known precipitants, for example anhydrous ethanol, isopropanol or acetone, and purified by multiple repetition of the process. Preferred solids comprise at least 10% by weight of carbonic acid diesters, preferably at least 30% by weight of carbonic acid diesters, and particularly preferably at least 50% by weight of carbonic acid diesters.

Such carbonic acid diesters can then, isolated solvent-free, be used for the coupling, for example for HESylation. In this case, then, no side reactions occur, as described above using EDC-activated acid.

Based on the preceding paragraphs, it is clear to one of skill in the art that the claimed carbonic acid diesters are soluble in the aprotic solvents for reasons discussed below. The phrase “the volume of the pre-activated carbonic diester in the aprotic solvent” followed by the term “preferred solutions” in the first reproduced paragraph above, clearly show that the claimed carbonic diesters form solutions with the aprotic solvents; hence they are aprotic-solvent-soluble. In addition, the statement that the carbonic acid diesters can be precipitated from the solution in aprotic solvents, from the second paragraph reproduced above, clearly means that they are dissolved in the aprotic solvents to start with, so that they can be precipitated by using known precipitants. A list of well known aprotic solvents is provided on page 10, lines 20-21.

With regard to the Examiner's assertion that there is no teaching in the instant specification that the carbonic diester of hydroxyethyl starch has a mean content of “1:1 to 10:1”, without acquiescing to the reasons for the rejection, Claim 61 has been amended by replacing the term “1:1” with the term “4:1”, rendering this rejection moot.

Based on all of the above, Claims 61 and 70, as amended, as well as all claims dependent directly or indirectly thereon, meet the requirements of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 61-66 under 35 U.S.C. §103(a) over Tessler, in view of Benedict

Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tessler, U.S. Re. 28,809 (hereinafter, "Tessler") in view of Benedict *et al.*, U.S. Pat. No.: 2,744,894 (hereinafter, "Benedict"). The Examiner asserted that Claims 61-66 differ from Tessler only by claiming that the starch component thereof is a hydroxyethyl starch (HES). However, the Examiner stated that Benedict teaches HES and therefore, cures the deficiency of Tessler.

Applicant respectfully disagrees with these assertions for the reasons discussed below.

Tessler teaches aqueous slurries or dispersions of starch which are reacted with imidazolides of carboxylic or sulfonic acids to yield starch ester derivatives. These starch products can be prepared in non-aqueous solvents or by a dry reaction process (Abstract of Tessler). Inter alia, carbonic diesters of starch, in which both alcohol residues are derived from starch, are disclosed (column 4, line 25 of Tessler).

Benedict refers to a process for producing hydroxyalkyl ether of a polysaccharide, hydroxyethyl starch (Claims 1, 2, column 2, line 16 of Benedict). However, carbonic diesters are not even mentioned in this reference.

In contrast to the teachings of Tessler, Claim 61, as amended, is directed to a carbonic diester of hydroxyethyl starch (HES), in which only one alcohol residue is derived from hydroxyethyl starch (HES) and the other is derived from a different alcohol having a molecular weight in the range from 80 to 500 g/mol. Therefore, even substitution of the starch residues of Tessler in the carbonic diesters by HES residues taught by Benedict, would not result in the subject-matter of Claim 61, as amended, because the other alcohol residue is derived from an alcohol having a molecular weight in the range from 80 to 500 g/mol, which is not taught by any of the cited references alone or in combination.

Finally, there is also no motivation to combine and modify the cited references since none of them deals with the underlying problem of the present invention, *i.e.*, the need for a coupling method which allows for coupling of polysaccharides to amino-containing active substances, in particular proteins, in purely aqueous systems, or else in a solvent mixture with water. Therefore, one of skill in the art looking to improve coupling of polysaccharides to the amino-containing active substances, in purely aqueous systems, or in a solvent mixture with

water would not even consider teachings of the cited reference, let alone combine those teachings.

Applicant's carbonic diesters, as claimed, are long-lasting and usable in methods for producing conjugates with active substances and they make possible, in a targeted manner, the *coupling of polysaccharides or their derivatives (e.g., hydroxyethyl starch as presently claimed) to amino-containing active substances*, in particular proteins, in purely aqueous systems, or else in a solvent mixture with water (cf. US 2006100176 A1: paragraph [0007]). The compounds of the claimed invention provide binding of an active substance as *quantitative* as possible, due to a covalent bonding to polysaccharides or polysaccharide derivatives, *e.g., hydroxyethyl starch as presently claimed* (cf. US 2006100176 A1: paragraph [0008]). At the same time, the claimed invention provides compounds which make a linkage of a polysaccharide or a derivative thereof to an active substance as *mild* as possible, so that the structure, the activity and the compatibility of the active substance is changed as little as possible by the reaction. For example, intra- and intermolecular crosslinking reactions is avoided using the claimed invention. Finally, the claimed invention provides methods, as simple and inexpensive as possible, for producing such compounds and coupling products of polysaccharides or polysaccharide derivatives (hydroxyethyl starch as presently claimed) to active substances (cf. 2006100176 A1: paragraph [0011]).

The advantages and beneficial properties of the claimed invention are further illustrated by the present examples. Example 1 shows the production of HES 10/0.4-carbonic diester of N-hydroxysuccinimide in a *very simple and effective manner*. Said HES 10/0.4-carbonic diester of N-hydroxysuccinimide is used for the production of HES 10/0.4-coupled myoglobin (Example 2), and HES 10/0.4-coupled amphotericin B (Example 3). In both reactions, *the yield* of the reaction is *greater than 90%*.

The carbonic diesters of the present invention are water soluble (due to the HES moiety) and soluble in aprotic solvents. Therefore, they can be easily reacted in solution without precipitation and thus they allow for very simple and highly efficient coupling of hydroxyethyl starch to amino-containing active substances, in particular proteins, in purely aqueous systems, or else in a solvent mixture with water.

These advantages and beneficial properties are neither disclosed nor suggested by the cited prior art. A carbonic diester of starch having two starch residues, as taught in Tessler, would not be a proper starting material for the coupling of polysaccharides to amino-containing active substances, in particular proteins, in purely aqueous systems, or in a solvent mixture with water because a carbonic diester having two starch residues would have two groups of an identical reactivity. The reactivity of the starch residues would be significantly lower than that of an alcohol residue having a molecular weight in the range from 80 to 500 g/mol, as presently claimed. Therefore, coupling of the pharmaceutical active substances to the carbonic diester having two starch residues would require more drastic reaction conditions, which in turn would result in more side reactions and more side products in a comparison with the method of the present invention. As further mentioned above, a hydroxyethyl starch (HES) residue is clearly different from a starch residue. In addition, an alcohol having a molecular weight in the range from 80 to 500 g/mol is also different from a starch residue.

Based on all of the above, Claim 61 and 70, as amended, are non-obvious over Tessler, in view of Benedict. Claims 62-66 and 71-79 depend directly or indirectly on Claims 61 and 70, and therefore, are also non-obvious. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Tessler, in view of Benedict are respectfully requested.

Rejection of Claims 61-66 under 35 U.S.C. §103(a) over Buysch, in view of Benedict

Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buysch *et al.*, (U.S. Pat. No.: 5,068,321) in view of Benedict. The Examiner asserted that Claims 61-66 differ from Buysch only by claiming that the starch component thereof is a hydroxyethyl starch (HES). However, the Examiner stated that Benedict teaches HES and therefore, cures the deficiency of Buysch.

Applicant respectfully disagrees with these assertions for the reasons discussed below.

Buysch teaches a process for the production of polysaccharide carbonates by acylation of polysaccharides with carbonic esters (Abstract of Buysch). Inter alia, starches, dextrans and ethyl cellulose are mentioned as suitable starting materials (column 3, lines 56, 64 of Buysch). However, carbonic diesters of hydroxyethyl starch (HES), in which only one alcohol residue is

derived from hydroxyethyl starch (HES) and the other is derived from a different alcohol having a molecular weight in the range from 80 to 500 g/mol, are not disclosed or suggested in Buysch.

Moreover, as explained in Buysch "it is also surprising that no cyclic carbonates are formed, something which is clearly difficult to avoid on the basis of existing results." (column 3, lines 40 to 45 of Buysch). In view of this statement, it is very surprising that the present invention, which uses a symmetric carbonate compound as a starting material, allows for a simple and very efficient production of carbonic diesters that have only one hydroxyethyl residue (Examples 1 to 3 of the instant application). Therefore, the disclosure of Buysch teaches away from the claimed invention.

The teachings of Benedict were discussed above, in the reply to the Rejection of Claims 61-66 under 35 U.S.C. § 103(a) over Tessler, in view of Benedict.

As stated above, Claim 61, as amended, is directed to a carbonic diester of hydroxyethyl starch (HES), in which only one alcohol residue is derived from hydroxyethyl starch (HES) and the other is derived from a different alcohol having a molecular weight in the range from 80 to 500 g/mol. Therefore, even a substitution of the starch residues in the carbonic diesters of Buysch by the HES residues taught by Benedict, would not result in the subject-matter of the present application as claimed in Claim 61, as amended, because the other alcohol residue is derived from an alcohol having a molecular weight in the range from 80 to 500 g/mol, which is not taught by any of the cited references alone or in combination.

Furthermore, there is no motivation to combine the cited references since none of them deals with the underlying problem of the present invention, *i.e.*, the need for a coupling method which allows for coupling of polysaccharides to amino-containing active substances, in particular proteins, in purely aqueous systems, or in a solvent mixture with water. Therefore, one of skill in the art looking to improve coupling of polysaccharides to amino-containing active substances, in purely aqueous systems, or in a solvent mixture with water would not even consider teachings of the cited reference let alone combine those teachings.

In addition, as discussed above, the instant invention, as claimed, possess many beneficial properties. These advantages are neither disclosed nor suggested by the cited references. Therefore, the claimed invention is non-obvious in view of the cited references.

Based on all of the above, Claims 61 and 70, as amended, are non-obvious over Buysch, in view of Benedict. Claims 62-66 and 71-79 depend directly or indirectly on Claims 61 and 70, and therefore, are also non-obvious. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Buysch, in view of Benedict are respectfully requested.

Rejection of Claims 61-66 under 35 U.S.C. §103(a) over Gaertner, in view of Benedict

Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaertner *et al.*, U.S. Pat. No.: 2,868,781(hereinafter, "Gaertner") in view of Benedict. The Examiner asserted that Claims 61-66 differ from Gaertner only by claiming that the starch component thereof is a hydroxyethyl starch (HES). However, the Examiner stated that Benedict teaches HES and therefore cures the deficiency of Gaertner.

Applicant respectfully disagrees with these assertions for the reasons discussed below.

Gaertner teaches biscarbohydrate *esters of aliphatic dicarboxylic acids* in which the carbohydrate is non-esterified and in which the carbohydrate is a saccharide containing no more than two saccharide units, and in which the dicarboxylate radical contains from 1 to 8 carbon atoms between the carboxyl groups, and on one of said carbon atoms there is substituted a radical of 5 to 20 carbon atoms (Claim 1 of Gaertner).

However, *carbonic diesters* are not taught or even disclosed in Gaertner. Accordingly, carbonic diesters of hydroxyethyl starch (HES), in which only alcohol residue is derived from hydroxyethyl starch (HES) and the other is derived from a different alcohol having a molecular weight in the range from 80 to 500 g/mol, are also not described in Gaertner.

The teachings of Benedict were discussed above, in the reply to the Rejection of Claims 61-66 under 35 U.S.C. §103(a) over Tessler, in view of Benedict.

Claim 61, as amended, is directed to a carbonic diester of hydroxyethyl starch (HES), in which only one alcohol residue is derived from hydroxyethyl starch (HES) and the other is derived from a different alcohol having a molecular weight in the range from 80 to 500 g/mol. Therefore, no modification of biscarbohydrate *esters of aliphatic dicarboxylic acids* of Gaertner, including a substitution of the starch by the HES residues of Benedict, would result in the subject-matter of the present application as claimed in Claim 61, as amended, because the Gaertner does not teach carbonic diesters, but different class of compounds: *esters of aliphatic*

*dicarboxylic acids*. Furthermore, the other alcohol residue in the claimed carbonic diesters is derived from an alcohol having a molecular weight in the range from 80 to 500 g/mol, which is not taught or disclosed by any of the cited references alone or in combination.

Claims 61 and 70, as amended, are non-obvious over Gaertner in view of Benedict, for the reasons discussed above. Claims 62-66 and 71-79 depend directly or indirectly on Claims 61 and 70, and therefore, are also non-obvious. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Gaertner, in view of Benedict are respectfully requested.

Requirements from the Decision issued in response to the Petition under 37 CFR 1.182 to correct the date of completion of The 35 U.S.C. 371 requirements

An English translation of the PCT application, a signed Supplemental Declaration and appropriate fees as requested in the Decision of July 22, 2009 are submitted herein. Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380.

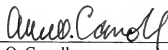
CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By



Alice O. Carroll

Registration No. 33,542

Telephone: (978) 341-0036

Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: April 29, 2011